REMARKS

Claims 1 to 22 as presented with applicants' paper of January 09, 2009, are currently pending. Claim 1 is the sole independent claim, and Claims 2 to 22 depend either directly or indirectly upon Claim 1.

The Office action reiterated the position that the subject matter of Claims 1 to 4, 6 to 8, 10 to 19, 21 and 22 was rendered unpatentable under 35 U.S.C. 103(a) by the teaching of ***Klimesch et al.*** (US 5,073,379) when taken in view of the disclosure of ***Thacharodi et al.*** (EP 0 960 620), asserting in particular that one of ordinary skill

- "*would know*" that crosslinked PVP is extrudable,
- "*would know*" that the amount of diluents in a pharmaceutical composition can be modified based on the desired functionality of the diluent, and
- "*would find it obvious*" to employ a high level of a disintegrant such as crosslinked PVP for fast disintegration and a low level for slower disintegration.[1)]

Applicants respectfully urge that the propositions are generalizations which do not apply in the pertinent technology in the asserted manner, or which cannot be applied in the technology underlying the process of ***Klimesch et al.***, or which do not apply under the particular circumstances here.

In principle, any particulate solid matter can be extruded including, e.g., sand. However, the process of ***Klimesch et al.*** involves extruding a polymer melt and *forming the still plastic extrudate* into a tablet. The reference also explains, for example, that the extrudable pharmaceutical mixtures which are processed in accordance with the reference "***are pasty and therefore extrudable due to the melting or softening of one or more components***."[2)] Extrudability in the context of the teaching of ***Klimesch et al.***, thus, requires more than merely the ability of the material to be conveyed through an extruder. A granular extrudate would not yield tablets in the shaping apparatuses, and thus would render the process of ***Klimesch et al.*** inoperable. It is therefore critical for the purposes of ***Klimesch et al.***'s process that the material exit the extruder in pasty, still plastic and thus moldable form. To ensure a pasty, plastic and thus moldable consistency of the extrudate, ***Klimesch et al.*** employ mixtures which comprise certain thermoplastic binder polymers, i.e., thermoplastic polymers which soften or melt at from 50 to 180°C.[3)]

1) Office action page page 13, lines 4 to 12.

2) Col. 3, indicated lines 1 to 6, of ***US 5,073,379***; emphasis added.

3) E.g., col. 3, indicated lines 6 to 29, of ***US 5,073,379***.

Crosslinked PVP is not a thermoplastic polymer and cannot, per se, be expected to form a paste under the extrusion conditions of the primary reference. In the terms which are used by ***Klimesch et al.***, crosslinked PVP per se, therefore, cannot be deemed "*extrudable*" as is asserted in the Office action. Example 3 of ***Klimesch et al.*** merely illustrates that certain amounts of crosslinked PVP may be incorporated into extrudable mixtures, i.e., an amount of 5.3%-wt. based on the amount of the binder polymer.[4] The example does not show or suggest that crosslinked PVP itself is capable of forming a pasty moldable extrudate.

It is a prerequisite of the process of ***Klimesch et al.*** that the extrudate be obtained in a cohesive, still plastic and thus moldable form. However, crosslinked PVP is not thermoplastic and thus cannot be expected to convey a pasty consistency to the extrudate. To the contrary, due to its lack of thermoplastic properties, an increase in the amount of crosslinked PVP in the mixture, at the expense of the amount of binder, is prone to undermine the capability of the binder polymer to "bind" the components of the mixture such that a cohesive, plastic and moldable extrudate is formed. Without appropriate binding, however, the mixture loses cohesion and granules are obtained instead of the pasty and moldable extrudate that is required for the purposes of the process of ***Klimesch et al.*** One of ordinary skill in the art therefore readily appreciates that, in the context of the process of ***Klimesch et al.***, the amount of auxiliaries other than the binder, e.g., crosslinked PVP, cannot be freely modified merely on the basis of their functionality.

In fact, ***Klimesch et al.*** specifically point out that conventional pharmaceutical auxiliaries may be incorporated in the mixture but limits the total amount of such auxiliaries to at most 100% by weight, based on the binder polymer.[5] Thus, ***Klimesch et al.*** specifically conveys that increasing the amount of auxiliaries at the cost of the amount of binder beyond a weight ratio of at most 1:1 is impracticable. Conventional auxiliaries which are mentioned in this context include, e.g., extenders (*i.e., diluents*) and disintegrants such as crosslinked PVP.

Considering that a granular, non-cohesive extrudate is unsuited for the purposes of ***Klimesch et al.***'s process, one of ordinary skill has no incentive to increase the amount of crosslinked PVP at the cost of the amount of binder beyond the at most 1:1 ratio because doing so may cause a loss of cohesion of the extrudate and render the process of ***Klimesch et al.*** inoperable. However, if a proposed modification would render the prior art invention which is being modified unsatisfactory

4) Col. 6, indicated lines 48 to 59, of ***US 5,073,379***.

5) Col. 4, indicated lines 30 to 40, of ***US 5,073,379***.

for its intended purpose, then there is no suggestion or motivation to make the proposed modification.[6]

The motivation to increase the amount of crosslinked PVP in the mixture of ***Klimesch et al.*** is lacking, independent of the desired function of the auxiliary, be it the extender/diluent properties, the stabilizing properties regarding pyridyl sulfinyl benzimidazoles addressed in ***Thacharodi et al.***, or the disintegrant properties of crosslinked PVP.

Diluting or extending properties are *inter alia* provided in the mixtures of ***Klimesch et al.*** by the binder polymer. Thus, dilution of the active ingredient in the preparation can readily be achieved by increasing the relative amount of the binder. Such a modification would not bear the risk of losing the pasty properties of the extrudate and thereby rendering the process of ***Klimesch et al.*** unsatisfactory. The stabilizing effects on pyridyl sulfinyl benzimidazoles addressed by ***Thacharodi et al.*** are obtained by any polymer which comprises vinylpyrrolidone monomer units.[7] Suitable polymers include thermoplastic vinylpyrrolidone polymers and one having ordinary skill will readily appreciate that the stabilizing effects can be realized by a thermoplastic binder polymer without risking to render the process of ***Klimesch et al.*** unsatisfactory. The non-thermoplastic properties of crosslinked PVP, together with the teaching of ***Klimesch et al.*** deter from increasing the amount of the disintegrant at the cost of the amount of binder beyond the at most 1:1 weight ratio as a loss in binding effectivity of the thermoplastic polymer would render the extrudate granular, and the mixture unsuitable for the purposes of the process of ***Klimesch et al.*** Also, one of ordinary skill will appreciate that conventional pharmaceutical preparations generally comprise disintegrants in amounts of, e.g., 2 to 20% by weight.[8] The amounts in which disintegrants are generally incorporated into conventional pharmaceutical preparations, therefore, also cannot direct one of ordinary skill in the pertinent technology to increase the amount of disintegrant relative to the amount of the binder in the mixture of ***Klimesch et al.*** to a weight ratio beyond the at most 1:1 ratio which is taught by ***Klimesch et al.*** The conclusion that, "*since the crosslinked PVP functions as a disintegrant/stabilizer/diluent, one of ordinary skill in the art would find it obvious to modify the level based on the desired function, i.e., high level for diluent and fast disintegration, low level for slower disintegration*"[9] is, therefore, deemed to lack the rational underpinning neces-

---

6) MPEP §2143.01 (V), Rev. 6, Sept. 2007, page 2100-140, citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

7) E.g., page 4, indicated line 39 to page 5, indicated line 4, of ***EP 0 960 620***.

8) E.g., col. 3, indicated lines 27 to 39, at indicated lines 34 to 36, of ***US 6,485,745***; copy enclosed.

9) Office action page page 13, lines 9 to 12.

sary to support a conclusion of obviousness[10] where the process involves forming a moldable cohesive composition from a mixture comprising from 50 to 99%-wt. of a crosslinked non-thermoplastic carrier and from 0.5 to 30%-wt. of a particular adjuvant.

The Office action also asserts, "*Thacharodi clearly teaches a high level of crosslinked PVP in Example 6 and this reference is properly combined with Klimesch because it is obvious to combine prior art elements according to known methods to yield predictable results.*"[11] However, neither Example 6 nor any other part of the secondary reference, teaches, suggests or implies that the ingredients in question in the pertinent amounts may be blended so as to form a cohesive, plastic and moldable extrudate as is mandated in accordance with the teaching of ***Klimesch et al.*** Since crosslinked PVP does not have binder properties it cannot reasonably be expected that the modified mixtures yield a plastic and moldable extrudate under the conditions of the process of ***Klimesch et al.*** The result of the proposed modification, therefore, is not predictable.

The mixtures addressed in the disclosure of ***Thacharodi et al.*** are "*in the form of a simple powder blend*" and the powder blend may be converted into granules. The application forms are obtained by filling the powder blend or the granules into enteric capsules,[12] and the reference points out that "*the process for the preparation of the present invention is simple, less time consuming and more economical than prior art processes*"[13] because it does not require:[14]

- steps for conversion of a powder blend into core units such as granules, pellets or tablets;
- the step of applying a subcoat over the core units; or
- additional pharmaceutical excipients.

Example 6 of ***Thacharodi et al.*** merely illustrates the preparation of a powder blend in which crosslinked PVP serves as a diluent and stabilizer, and the conversion thereof into granules. Accordingly,

1) 20 wt.-parts of omeprazole and 100 wt.-parts of Kollidon® CL (*crosslinked PVP*) were mixed to form the powder blend;
2) 20 wt.-parts of Akomed R® and 10 wt.-parts of Gelucire® 33/01 were heated to 60°C for 20 minutes, stirred well and then cooled to 30°C; and

10) *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)(quoting Kahn, 441 F.3d at 2006).
11) Office action page page 13, lines 12 to 15.
12) Page 3, indicated lines 12 and 15, of ***EP 0 960 620.***
13) Page 3, indicated lines 23 and 24, of ***EP 0 960 620.***
14) Page 3, indicated lines 16 to 21, of ***EP 0 960 620.***

3) 120 wt.-parts of the powder blend obtained in (1) were granulated with 30 wt.-parts of the liquid obtained in (2).

The example neither illustrates nor suggests that the components, in the requisite amounts, may be blended so as to form a cohesive plastic and thus moldable extrudate as is required in accordance with the teaching of ***Klimesch et al.*** An extrudate in form of granules as are obtained in Example 6 of ***Thacharodi et al.***, however, would render the mixture unsuited for the purposes of the process of ***Klimesch et al.***

In light of the foregoing and applicants' arguments presented with the paper of August 12, 2009, the teaching of ***Klimesch et al.*** when taken in view of the disclosure of ***Thacharodi et al.*** cannot be deemed to render a process obvious which involves, inter alia, *forming a moldable cohesive composition* which comprises

a) 50 to 99.4% by weight of at least one crosslinked non-thermoplastic carrier,

b) 0.5 to 30% by weight of at least one adjuvant selected from the group consisting of thermoplastic polymers, lipids, sugar alcohols, sugar alcohol derivatives and solubilizers and

c) 0.1 to 49.5% by weight of at least one active ingredient,

as is required in accordance with applicants' Claims 1 to 4, 6 to 8, 10 to 19, 21 and 22. It is therefore respectfully requested that the rejection be withdrawn. Favorable action is solicited.

The Office action also reiterated the position that the subject matter of Claim 5 was rendered unpatentable under 35 U.S.C. 103(a) by the teaching of ***Klimesch et al.*** when taken in view of the disclosure of ***Thacharodi et al.*** and further in view of the disclosure of ***Endicott et al.*** (**US 3,087,860**). With a particular view to the additional reference, the Office action noted, *"Endicott teaches adjuvants such as sorbitol **and** mannitol (Col. 3, lines 67-70) and teaches that a drug-plastic combination can be **mixed and extruded** (Col. 4, lines 21 -23)."*[15]

The procedure of ***Endicott et al.*** involves compressing a particulate composition which *inter alia* comprises a drug-plastic mixture and subsequently fusing the plastic particles by vapor treatment with a volatile organic solvent which softens the surface of the plastic particles.[16] The consistency of an extrudate which is obtained when mixing and extruding the drug-plastic combination, i.e., cohesive or granular, therefore is of no concern for the purposes of ***Endicott et al.***'s process. As noted above, however, the consistency of the extrudate is of utmost importance for the

15) Office action page 14, lines 1 to 3.

16) E.g., col. 2, indicated lines 17 to 31, of ***US 3,087,860***.

success of the process of ***Klimesch et al.*** and a granular extrudate would render the process of ***Klimesch et al.*** unsatisfactory. ***Endicott et al.*** are silent as to the consistency of the extrudate. As such, the reference cannot be deemed to convey information which would direct a person of ordinary skill to a process which involves *forming a moldable cohesive composition* comprising the pertinent ingredients in the respective amounts set forth in Claim 1 and incorporated into Claim 5 by reference. At best, ***Endicott et al.*** merely provide that sorbitol and mannitol may be incorporated into the mixture of ***Klimesch et al.*** However, in doing so a person of ordinary skill in the art would not be directed to reduce the amount of binder polymer relative to the total amount of pharmaceutical auxiliaries in general, and in particular relative to the amount of cross-linked, non-thermoplastic carriers. Thus, the teaching of ***Klimesch et al.*** when taken in view of the disclosure of ***Thacharodi et al.*** and further in view of the disclosure of ***Endicott et al.*** cannot render the subject matter of Claim 5 unpatentable under Section 103(a).

It is therefore respectfully requested that the rejection be withdrawn. Favorable action is solicited.

Last but not least, the Office action reiterated the position that the subject matter of Claims 9 and 20 was rendered unpatentable under 35 U.S.C. 103(a) by the teaching of ***Klimesch et al.*** when taken in view of the disclosure of ***Thacharodi et al.*** and further in view of the disclosure of ***Goertz et al.*** (**US 4,801,483**). With a particular view to the additional reference, the Office action noted, "*Goertz teaches a process for the preparation of solid pharmaceutical forms by mixing one or more pharmaceutical active compounds with one or more fusible, pharmacologically tolerated binders and subjecting the mixture to extrusion and shaping, wherein the fusible binder used is a solvent-free NVP polymer (Col. 1, line 64 to Col. 2, line 4). 'Shaping may be effected by injection molding or by extrusion followed by shaping of the plastic extrudate, for example by hot-face cutting to give granules or molding to give tablets . . . cold-face cutting is also suitable and may be followed by pressing of the granules to give tablets' (Col. 5, lines 11 -20).*"[17]

The process of ***Goertz et al.*** is similar to the process of ***Klimesch et al.*** in that solid pharmaceutical forms are prepared by mixing an active ingredient with a polymeric binder at an elevated temperature, i.e., in an extruder, and shaping the still plastic, moldable extrudate, or by injection molding. Also similar to ***Klimesch et al.***, ***Goertz et al.*** note that conventional auxiliaries, including extenders (*diluents*) and disintegrating agents (*i.e., crosslinked PVP*), may be incorporated into the

17) Office action page 14, lines 1 to 3.

mixtures in a total amount of up to 100% by weight, based on the binder polymer.[18] As is the case in the teaching of ***Klimesch et al.***, the success of the process of ***Goertz et al.*** depends upon forming a still plastic and thus moldable extrudate. The disclosure of the additional reference, thus, also fails to direct a person of ordinary skill to a process which involves *forming a moldable cohesive composition* comprising the pertinent ingredients in the respective amounts set forth in Claim 1 and incorporated into Claims 9 and 20 by reference. At best, ***Goertz et al.*** merely provide that the cohesive, plastic extrudate of ***Klimesch et al.*** may be injection molded, or the moldable extrudate may be cut into granules. However, in doing so a person of ordinary skill in the art would not be directed to reduce the amount of binder polymer relative to the total amount of pharmaceutical auxiliaries in general, and in particular relative to the amount of cross-linked, non-thermoplastic carriers.

The Office action asserts that "*Thacharodi teaches the high level of crosslinked PVP in granular formulations and one of ordinary skill in the art would look to Goertz for the formation of tablets from granules.*"[19] However, the pertinent difference between the disclosures of ***Thacharodi et al.*** and ***Goertz et al.*** resides in the manner in which the granules are obtained. ***Thacharodi et al.*** employ a powder blend and granulate the powder blend with certain glycerides. The procedure does not involve forming a cohesive, moldable extrudate as is required in accordance with the teaching of ***Klimesch et al.*** and in accordance with the disclosure of ***Goertz et al.*** Also, nothing in the disclosure of ***Thacharodi et al.*** teaches, or reasonably suggests or implies that the components in question in the pertinent amounts may be blended so as to form a cohesive, plastic and moldable extrudate as is required for the success of the processes of ***Klimesch et al.*** and of ***Goertz et al.*** Thus, the teaching of ***Klimesch et al.*** when taken in view of the disclosure of ***Thacharodi et al.*** and further in view of the disclosure of ***Goertz et al.*** cannot render the subject matter of Claims 9 and 20 unpatentable under Section 103(a).

It is therefore respectfully requested that the rejection be withdrawn. Favorable action is solicited.

CONCLUSION

In light of the foregoing remarks the application is in good condition for allowance, and favorable action is respectfully solicited.

18) Col. 5, indicated lines 38 to 48, of ***US 4,801,460***.

19) Office action page 18, lines 1 to 3.